Managing Diabetes: Lessons from Type 1 Diabetes Mellitus

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Glycaemic control is a key component of the successful management of Type 1 and Type 2 diabetes mellitus. Hypoglycaemia is the limiting factor in the management of diabetes because current glucose-lowering regimens are imperfect, defences against decreasing glucose levels in Type 1 and probably Type 2 diabetes are compromised, and low glucose levels have a devastating effect on the brain. Usually, hypoglycaemia precludes the maintenance of normal glucose levels. However, attempts to circumvent the barrier of hypoglycaemia safely are worthwhile because shifting glucose levels towards the non-diabetic range reduces the long-term complications of diabetes. Patient education and empowerment, appropriate self-monitoring of blood glucose, flexible drug regimens, individualized and prudent glycaemic goals, and ongoing professional support are fundamental. Iatrogenic hypoglycaemia is the result of the interplay between excess insulin and compromised glucose counter-regulation in Type 1 and probably Type 2 diabetes. Conventional and newly recognized risk factors must be addressed. Relative or absolute excess insulin occurs when: insulin (or insulin secretagogue) doses are excessive, ill-timed or of the wrong type; the influx of exogenous glucose, endogenous glucose production or insulin clearance are decreased; and insulin-independent glucose utilization or insulin sensitivity are increased. The drug regimen, food ingestion, exercise and alcohol use are under the direct control of the patient and the healthcare provider, and regimen adjustments can be used to address insulin sensitivity and clearance. Unfortunately, these conventional risk factors explain only a minority of episodes of severe hypoglycaemia and therefore the issue of compromised glucose counter-regulation must also be addressed. It is imperative to investigate the patient history for hypoglycaemia unawareness because short-term (e.g. 2 weeks) scrupulous avoidance of hypoglycaemia can restore awareness and improve defective glucose counter-regulation. Until methods of perfect insulin replacement or release are developed, improved regimens and pharmacological methods to minimize hypoglycaemia particularly during the night can be used safely to improve overall glycaemic control.

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Introduction

Successful management of diabetes mellitus is accomplished by a well informed and empowered patient who receives comprehensive preventive and therapeutic medical care. Glycaemic control is one key component of the successful management of diabetes and the focus of this brief review.

The Limiting Factor in the Management of Diabetes

Diabetes would be a straightforward disease to treat, were it not for hypoglycaemia and its devastating effects on the brain. Sufficient insulin (or amounts of insulin secretagogue) to reduce plasma glucose levels to the non-diabetic range or below would eliminate symptoms, undoubtedly prevent the long-term specific complications (retinopathy, nephropathy and neuropathy) and probably reduce the risk of atherosclerosis to baseline. However, the effects of hypoglycaemia on the brain are devastating and the management of diabetes is therefore complex.[1]

The importance of glycaemic control is well established in people with diabetes for preventing or delaying the specific long-term complications.[2–4] Nonetheless, over a period of an average of only 6.5 years, diabetic retinopathy developed or progressed in 14 % (100 of 711) of

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patients with Type 1 diabetes treated intensively (compared with 32 % of those patients treated conventionally) in the Diabetes Control and Complications Trial (DCCT).[3] Similarly, diabetic nephropathy and neuropathy developed or progressed in many patients treated intensively (albeit again at lower rates than in patients treated conventionally). The occurrence of these complications in a substantial proportion of people with Type 1 diabetes over a short period of time despite aggressive treatment aimed at reducing circulating glucose levels was mostly, perhaps exclusively, the result of the inability to achieve euglycaemia in the majority of patients. Fewer than 5 % of patients treated intensively in the DCCT maintained haemoglobin A_{1c} (HbA_{1c}) at normal levels (<6.05 %), with a median level of 7.2 %. The mean (± sd) capillary blood glucose level was 8.6 ± 1.7 mmol·l^{-1} (155 ± 30 mg·dl^{-1}), approximately twice that of non-diabetic individuals. Euglycaemia could not be achieved safely because of the barrier of iatrogenic hypoglycaemia. The incidence of severe hypoglycaemia (i.e. requiring the assistance of another person) was inversely (and exponentially) related to HbA_{1c} levels and more than three-fold higher in patients treated intensively. Clearly, even under the optimized conditions of the DCCT iatrogenic hypoglycaemia is the limiting factor in the management of Type 1 diabetes.[1] As shown in the United Kingdom Prospective Diabetes Study (UKPDS), this is also the case in Type 2 diabetes.[5]

People with Type 1 diabetes attempting to achieve glycaemic control have frequent episodes of asymptomatic hypoglycaemia. Blood glucose levels may be less than 3.0 mmol·l^{-1} (54 mg·dl^{-1}) as often as 10 % of the time. Type 1 diabetic patients have an average of two episodes of symptomatic hypoglycaemia per week and approximately one episode of severe hypoglycaemia per year often with a seizure or coma.[1–3]

Hypoglycaemia is generally less frequent in people with Type 2 diabetes; over the first 6 years of the UKPDS 3.3 % of patients with Type 2 diabetes treated aggressively with a sulphonylurea and 11.2 % of patients treated aggressively with insulin had at least one episode of severe hypoglycaemia.[6] These proportions are considerably lower than the 65 % of patients with Type 1 diabetes treated intensively for an average of 6.5 years in the DCCT[3] who experienced at least one episode of severe hypoglycaemia. Nonetheless, as Type 2 diabetes progresses over time, hypoglycaemia becomes more frequent, and limiting.[4,5] Notably, the rates of severe hypoglycaemia were similar in groups of Type 1 and Type 2 diabetic patients matched for duration of insulin therapy.[7] In contrast to insulin-induced hypoglycaemia in Type 1 diabetes, from which complete recovery occurs in the vast majority of instances, sulphonylurea-induced hypoglycaemia in Type 2 diabetes has been associated with mortality rates as high as 10 % and permanent neurological sequelae in as many as 5 % of survivors.[8]

Glucoregulation in Diabetes

The physiological mechanisms that normally maintain systemic glucose balance despite diverse rates of exogenous glucose influx (e.g. fasting vs. feeding) or endogenous glucose efflux (e.g. rest vs. exercise), and prevent hyperglycaemia or hypoglycaemia (thus ensuring a continuous supply of glucose to the brain) are complex. Hormones, neurotransmitters and substrates are all part of the physiological mechanisms involved.[9] However, three hormones—insulin, glucagon and, at least in the absence of increments in glucagon, adrenaline—stand high in the hierarchy of the redundant glucoregulatory factors.[9] The secretion of all three of these hormones, not just insulin, is reduced in established Type 1 (C-peptide negative) diabetes.[1]

Insulin deficiency is the proximate cause of clinical Type 1 diabetes and exogenous insulin must therefore be administered. As the patient becomes totally insulin deficient and dependent on exogenous insulin, the first defence against decreasing glucose levels (i.e. reduced insulin secretion) is lost. Concomitantly, the second defence, an increase in glucagon secretion, is also lost.[10–12] Therefore, glucose counter-regulation is altered fundamentally in established Type 1 diabetes. Furthermore, the adrenaline response to decreasing glucose levels is reduced in most patients with established Type 1 diabetes,[11,12] which is a critical pathophysiological event because the frequency of severe hypoglycaemia during intensive therapy is increased 25-fold or more in this category of Type 1 diabetic patients—the syndrome of 'defective glucose counter-regulation'—compared with patients who have absent glucagon but normal adrenaline responses.[13,14] The reduced sympathochromaffin (sympathoadrenal) response to decreasing glucose levels also underlies the syndrome of 'hypoglycaemia unawareness'—loss of the warning, mostly (if not completely) autonomic symptoms of developing hypoglycaemia—that is also associated with a substantially increased frequency of severe hypoglycaemia in Type 1 diabetes.[15] Substantial evidence now exists that hypoglycaemia unawareness and the reduced adrenaline component of defective glucose counter-regulation are the result of recent antecedent iatrogenic hypoglycaemia.[1,16–19]

Iatrogenic hypoglycaemia in Type 1 diabetes results from the interplay of absolute or relative insulin excess (which must occur from time-to-time because of the imperfections of all insulin replacement regimens) and compromised glucose counter-regulation ('defective glucose counter-regulation' and 'hypoglycaemia unawareness').[1] The concept of 'hypoglycaemia-associated autonomic failure' in Type 1 diabetes[1,12] (Figure 1) posits that periods of excessive relative or absolute therapeutic insulin lead to episodes of iatrogenic hypoglycaemia in the setting of absent glucagon secretory responses to decreasing glucose levels. These episodes of iatrogenic hypoglycaemia in turn cause reduced autonomic responses (adrenomedullary and sympathetic neural, and

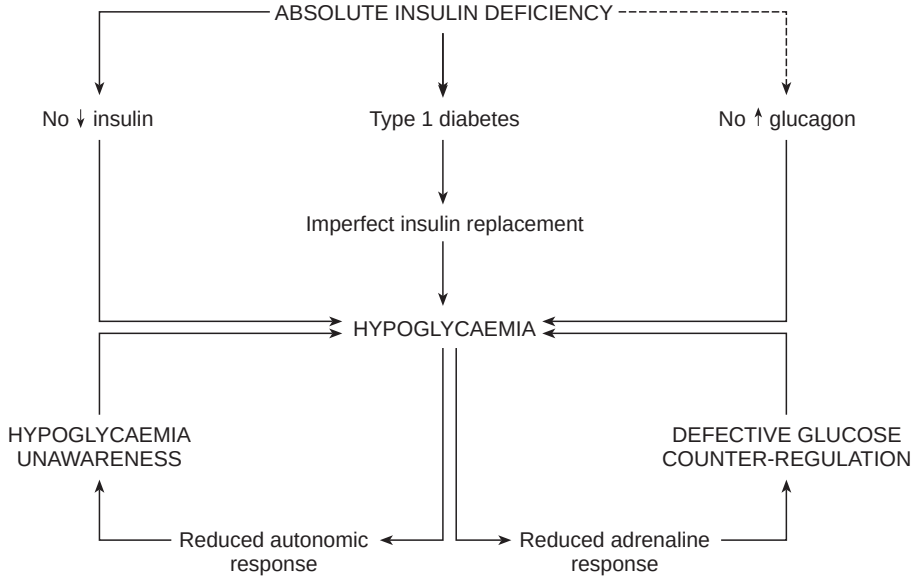

Figure 1. Schematic diagram of the concept of hypoglycaemia-associated autonomic failure in Type 1 diabetes and the role of episodes of iatrogenic hypoglycaemia in the pathogenesis and perpetuation of the clinical syndromes of hypoglycaemia unawareness and defective glucose counter-regulation

parasympathetic neural) to any subsequent decrease in glucose levels, and the decreased autonomic responses result in reduced symptoms that warn of hypoglycaemia development (i.e. hypoglycaemia unawareness) and impaired physiological defences against developing hypoglycaemia (i.e. defective glucose counter-regulation). A vicious cycle of recurrent hypoglycaemia is therefore created and perpetuated. Perhaps the most compelling support for this concept is that hypoglycaemia unawareness, and probably the reduced adrenaline component of defective glucose counter-regulation, are reversible in the majority of patients with Type 1 diabetes by relatively short-term (e.g. 2 weeks) scrupulous avoidance of iatrogenic hypoglycaemia.[16–19]

The extent to which these pathophysiological concepts developed in Type 1 diabetes can be extrapolated to Type 2 diabetes is uncertain. In the early stages of Type 2 diabetes, patients have relative rather than absolute insulin deficiency. Nonetheless, reduced glucagon responses to hypoglycaemia have been reported in patients with Type 2 diabetes.[19,20] Since progressive loss of insulin secretion occurs over time in Type 2 diabetes,[6] the glucagon response may be lost in patients at the insulin deficient end of the spectrum. Because the reduced adrenaline response to hypoglycaemia is the result of recent antecedent hypoglycaemia in Type 1 diabetes, a similar phenomenon may occur during aggressive therapy of Type 2 diabetes. Thus, defective glucose counter-regulation and hypoglycaemia unawareness similar to that observed in Type 1 diabetes may occur in patients with long-term Type 2 diabetes. This is consistent with the finding that the frequency of severe iatrogenic hypoglycaemia is similar in patients with Type 2 and Type 1 diabetes matched for duration of insulin therapy.[7] However, compromised glucose counter-regulation remains to be documented systematically in Type 2 diabetes.

Theoretically, monotherapy with drugs that increase sensitivity to endogenous insulin (e.g. biguanides or thiazolidinediones) or delay carbohydrate digestion (e.g. α-glucosidase inhibitors) should not cause hypoglycaemia. If these drugs decrease plasma glucose levels to the low physiological range, insulin secretion would be expected to decline and thus prevent development of hypoglycaemia. However, a six-fold increase in the frequency of severe hypoglycaemia with metformin treatment compared with diet-treated patients with Type 2 diabetes has been reported.[6] Such drugs may well increase the risk of hypoglycaemia when used in combination with insulin or an insulin secretagogue (e.g. a sulphonylurea or a non-sulphonylurea that stimulates insulin secretion).

Relevance to the Management of Diabetes

Conventional risk factors for iatrogenic hypoglycaemia are based on the premise that therapeutic insulin excess is the sole determinant of risk.[1] Relative or absolute insulin excess occurs when:

- Insulin (or insulin secretagogue) doses are excessive, ill timed or of the wrong type and therefore the drug regimen should be tailored to the individual patient. With a basal/bolus insulin regimen, use of the more rapid acting insulin lispro with meals reduces the frequency of nocturnal hypoglycaemia in Type 1 diabetes.[22,23] In general, long-acting sulphonylureas are more likely to cause iatrogenic hypoglycaemia than short-acting sulphonylureas and other short-

acting insulin secretagogues. In patients with Type 2 diabetes advanced biological age, malnutrition, and renal or hepatic dysfunction increase the risk of hypoglycaemia.[1]

- The influx of exogenous glucose is decreased, e.g. during an overnight fast or following a missed meal or snack.
- Insulin-independent glucose utilization is increased, e.g. during physical exercise.
- Endogenous glucose production is decreased, e.g. following alcohol ingestion in the setting of glycogen depletion.
- Sensitivity to insulin is increased, e.g. during effective intensive therapy, in the middle of the night, following exercise, after weight loss or during therapy with a drug that increases hepatic or muscle sensitivity to insulin.
- Insulin clearance is decreased, e.g. with renal failure.

These conventional risk factors must be considered when attempts to achieve glycaemic control become limited by iatrogenic hypoglycaemia in a patient, because the resultant adjustments may permit improved overall glycaemic control while minimizing the frequency of hypoglycaemia. However, these conventional risk factors explain only a minority of episodes of severe hypoglycaemia, at least in Type 1 diabetes.[24] To understand the pathogenesis of most hypoglycaemic episodes iatrogenic hypoglycaemia must be viewed as the result of the interplay of insulin excess and compromised glucose counter-regulation, at least in Type 1 diabetes. While formally assessing individual patients for defective glucose counter-regulation is not practical, the history for hypoglycaemia unawareness must be investigated. In Type 1 diabetic patients with hypoglycaemia unawareness (who undoubtedly also have defective glucose counter-regulation), awareness can be restored (and adrenaline secretion increased) usually by a relatively short period (e.g. 2 weeks) of scrupulous avoidance of iatrogenic hypoglycaemia.[16–19] The use of this short-term measure breaks the cycle of hypoglycaemia and permits safer intensive therapy in patients with Type 1 diabetes and perhaps those with Type 2 diabetes.

To achieve glycaemic control safely we must learn to replace or release insulin in a more physiological fashion, to prevent, correct or compensate for compromised glucose counter-regulation, or both.[1] Intensive therapy of Type 2 diabetes with an implantable insulin pump has been shown to reduce the frequency of hypoglycaemia.[25] If the risk of nocturnal hypoglycaemia could be reduced, improved and relatively safe glycaemic control should be possible during the day. While conventional bedtime snacks should be used, they can exert an inconsistent glycaemic effect and are effective only during the first half of the night.[26] To overcome this problem, administration of uncooked corn starch at bedtime has been advocated[27] but its unpalatability limits its use to small doses (e.g. 5.0 g). Alternative approaches, based on the pathophysiology of glucose counter-regulation in Type 1 diabetes, include bedtime administration of the glucagon-releasing amino acid alanine or of the adrenaline-simulating β_2-adrenergic agonist terbutaline. These have been shown to prevent nocturnal hypoglycaemia more effectively than a conventional bedtime snack in patients with Type 1 diabetes.[26] Again, the extent to which these approaches apply to patients with Type 2 diabetes is unknown. In theory, the use of an insulin secretagogue that releases insulin rapidly but only transiently with meals in patients with sufficient residual insulin secretion may reduce the risk of iatrogenic hypoglycaemia.[28]

The quest for glycaemic control is empirical in each individual person with diabetes. In practice, the treatment regimen is accelerated until the barrier of hypoglycaemia is reached. Then the regimen is adjusted as a whole to circumvent that barrier and maintain the best glycaemic control possible in the course of the patient's diabetes. In the setting of patient education and empowerment, appropriately frequent self-blood glucose monitoring, flexible drug regimens, individualized and prudent glycaemic goals and ongoing professional support may achieve acceptable glycaemic control in many patients. Nonetheless, improved approaches to the management of diabetes are needed urgently.

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